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In Vitro Effects of Cerium Vanadate ($CeVO_4$) Derivatives on Paraoxonase (PON1) Enzyme

Yasin Onay[1] · **Gülşah Çelik Gül**[2] · **Figen Kurtuluş**[3] · **Mine Nazan Kerimak-Öner**[4] · **Tuna Demirci**[5] · **Mustafa Oğuzhan Kaya**[6,7]

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Abstract

Cerium vanadate ($CeVO_4$)–based materials have attracted attention due to their diverse physicochemical and biological properties; however, their interactions with detoxification-related enzymes remain insufficiently characterized. This study evaluated the *in vitro* effects of alkaline earth metal–doped $CeVO_4$ derivatives (Be, Mg, Ca, Sr, and Ba) on human serum paraoxonase-1 (PON1) paraoxonase activity. PON1 was purified from human serum by hydrophobic interaction chromatography (Sepharose 4B–L-tyrosine–1-naphthylamine), and enzymatic activity was measured spectrophotometrically using paraoxon as the substrate. Inhibitory effects were assessed across multiple concentrations, and IC_{50} values were determined from concentration–response curves. All derivatives exhibited concentration-dependent inhibition of PON1 activity, with IC_{50} values ranging from 117 to 213 µM. Mg- and Ba-doped $CeVO_4$ derivatives demonstrated the strongest inhibition at higher doping ratios, whereas Ca-doped derivatives showed reduced inhibitory potency with increasing substitution levels. These findings indicate that dopant identity and concentration significantly influence the interaction between $CeVO_4$ derivatives and PON1. The study provides insight into metal oxide–enzyme interactions and highlights the importance of dopant-dependent effects in evaluating the biological and potential toxicological behavior of engineered vanadate-based materials.

Keywords Paraoxonase-1 (PON1) · Cerium vanadate ($CeVO_4$) · Alkaline earth metal doping · Enzyme inhibition · IC_{50}

1 Introduction

Serum paraoxonase-1 (PON1; EC 3.1.8.1) is a liver-derived, calcium-dependent enzyme that circulates predominantly in association with high-density lipoprotein (HDL) (Fig. 1). Epidemiological and experimental evidence indicates an inverse relationship between HDL levels and the progression of atherosclerosis, and HDL has been widely recognized for its ability to counteract oxidative processes implicated in atherogenesis [1]. Beyond its role in reverse cholesterol transport, HDL contributes to vascular protection by limiting oxidative modification of low-density lipoprotein (LDL), a central event in the initiation and advancement of atherosclerotic lesions [2–4].

Within this framework, PON1 has attracted substantial attention as a major contributor to the antioxidant capacity of HDL [1, 5]. Purified PON1 has been shown to attenuate copper-induced oxidation of both HDL and LDL, reflected by prolongation of the lag phase and reduced accumulation of lipid peroxides and reactive aldehydes; conversely,

✉ Mustafa Oğuzhan Kaya
m.oguzhankaya@gmail.com

[1] Graduate School of Natural and Applied Sciences, Department of Chemistry, Siirt University, Siirt, Turkey

[2] Project Coordination Office, Balikesir University, Balikesir, Turkey

[3] Faculty of Arts and Sciences, Department of Chemistry, Balikesir University, Balikesir, Turkey

[4] Department of Medicinal and Aromatic Plants, İzmit Technical College, Kocaeli University, Kocaeli, Turkey

[5] Scientific and Technological Research Application and Research Center, Düzce University, Düzce, Turkey

[6] Faculty of Arts and Sciences, Department of Chemistry, Kocaeli University, Kocaeli, Turkey

[7] Faculty of Veterinary Medicine, Department of Biochemistry, Siirt University, Siirt, Turkey

Fig. 1 Serum paraoxonase-1 complexed with 2-hydroxyquinoline, obtained via directed evolution at pH 6.5 [5]

pharmacological antagonists of PON1 diminish these protective effects [6–9]. Although the precise molecular basis of PON1-mediated antioxidant activity remains incompletely defined, experimental observations such as loss of protection after heat inactivation and evidence from PON1-deficient models support an essential role of PON1 in the antioxidative properties of HDL [10–13].

Importantly, PON1 is a multifunctional enzyme. In addition to its antioxidant-associated actions, PON1 exhibits paraoxonase activity capable of hydrolyzing organophosphate oxon metabolites (e.g., paraoxon, the toxic metabolite of parathion). This catalytic function contributes to detoxification of organophosphate pesticides and nerve agents and displays marked interindividual variability driven in part by common genetic polymorphisms (notably Q192R and L55M), as well as modulation by oxidative stress, inflammation, diet, pharmaceuticals, and environmental exposures [14, 15]. Reduced paraoxonase activity has therefore been associated with increased susceptibility to organophosphate toxicity and may intersect with oxidative stress-related disease pathways, supporting the relevance of targeting PON1 paraoxonase activity in toxicological and cardiovascular contexts.

Vanadate compounds comprise inorganic vanadium species that can exist in multiple oxidation states (from +3 to +5) and have been investigated extensively due to their broad biochemical reactivity and biological effects [16]. The toxicity profile of vanadium may be influenced by interactions with other elements, and a range of studies has examined vanadium compounds and their biological interactions [17–22]. Cerium vanadate ($CeVO_4$), a rare-earth orthovanadate belonging to the ABX_4 family, has attracted interest because both the host lattice and compositional modifications (including doping) can substantially alter physicochemical properties and biological responses [23–35]. Given the pivotal role of paraoxonase-1 in organophosphate detoxification and oxidative stress–related mechanisms, and in light of the capacity of doped cerium vanadate ($CeVO_4$) materials to modulate biological activity, alkaline earth metal–doped $CeVO_4$ derivatives (Be, Mg, Ca, Sr, and Ba) were synthesized to enable a focused evaluation of their inhibitory interaction with PON1 paraoxonase activity *in vitro* [13, 14, 23].

Given the established role of PON1 in organophosphate detoxification and oxidative stress–related processes, together with evidence that alkaline earth metal incorporation can influence the physicochemical and biological characteristics of vanadate-based materials, alkaline earth metal–doped $CeVO_4$ derivatives (Be, Mg, Ca, Sr, and Ba) were prepared to examine their effects on PON1 catalytic activity under *in vitro* conditions [23, 35].

The present study systematically evaluated the impact of cerium vanadate ($CeVO_4$) derivatives on PON1 activity, focusing specifically on their ability to inhibit the enzyme's paraoxon-hydrolyzing function. By establishing concentration–response relationships for the synthesized compounds, we sought to clarify the biochemical implications of $CeVO_4$–PON1 interactions and to assess their potential significance within cardiovascular and toxicological settings.

2 Materials and methods

2.1 Materials

Sepharose-4B, L-tyrosine, 1-naphthylamine, paraoxon, protein assay reagents, ceric sulfate and vanadium oxide were all obtained from Sigma Chem. Co. (Milan/Italy). All other chemicals used were of analytical grade and obtained from Sigma Chem. Co. (Darmstadt/Germany). Human discarded blood samples were provided from Siirt Government Hospital.

2.2 Methods

2.2.1 Synthesis of the $CeVO_4$ Derivatives

To produce $CeVO_4$, cerium sulfate and sodium orthovanadate were used. The synthesis involves mixing cerium sulfate and Na_3VO_4 in a 1:1 molar ratio and grinding them in an agate mortar, then microwave heating in a conventional oven (2.45 GHz, 850 W) for 10 min. Doping agents such as Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} were added to the base material at percentages of weight of 0.1, 0.5, 1, 2, 4, 6, 8, and 10, followed by a two-hour heat treatment at 800 °C using recognized techniques [36].

2.2.2 Purification of PON1 from Human Serum

As detailed in our previous research, serum samples were obtained from fresh human blood collected in anticoagulant-free dry tubes. To separate the serum, the blood was subjected to centrifugation at 26,916 g for 15 min. The initial step of enzyme isolation involved ammonium sulfate fractionation (60–80%). The resulting protein precipitate was recovered via centrifugation at 26,916 g for 20 min and subsequently reconstituted in a 100 mM Tris-HCl buffer adjusted to pH 8.0 [37]. The crude enzyme extract was further purified using hydrophobic interaction chromatography on a specialized column. This column consisted of Sepharose-4B integrated with L-tyrosine-1-naphthylamine, synthesized according to the protocol described by Sinan et al. [38]. In brief, a 1:1 aqueous suspension of Sepharose-4B was activated using 10% CNBr. During this process, the mixture was maintained at pH 11 in an ice bath for approximately 8–10 min. The activation was terminated by filtering the gel through a Buchner funnel, followed by washing with a chilled 0.1 M $NaHCO_3$ buffer (pH 10.0). L-tyrosine was then covalently attached to the activated Sepharose-4B by introducing a saturated L-tyrosine solution in 0.1 M $NaHCO_3$ (pH 10.0). This coupling reaction was carried out under magnetic stirring for 90 min. To eliminate unbound L-tyrosine, the gel was washed thoroughly with distilled water. The final hydrophobic matrix was produced through the diazotization of 1-naphthylamine and its subsequent coupling to the L-tyrosine-Sepharose-4B complex. The pH was regulated to 9.5 using 1 M NaOH, and the mixture was stirred for 3 h at ambient temperature.

The resulting red Sepharose derivative was washed sequentially with water and an excess of 0.05 M Tris-sulfate (pH 7.5). Finally, the chromatographic column was equilibrated with 0.1 M Na_2HPO_4 buffer (pH 8.0) containing 1 M ammonium sulfate [37]. Paraoxonase was eluted using a linear ammonium sulfate gradient (ranging from 0.1 M Na_2HPO_4 buffer from 0.1 M Na_2HPO_4 buffer with ammonium sulfate to without ammonium sulfate at pH 8.0). To preserve its catalytic activity, the purified PON1 enzyme was stored at +4 °C in the presence of 2 mM $CaCl_2$ [37, 39].

2.2.3 PON1 Enzyme Assay

The enzymatic activity of PON1 against the paraoxon substrate was determined spectrophotometrically following the protocol established by Gan et al. [40]. The assay was conducted using a BioTek spectrophotometer, where the formation of p-nitrophenol was monitored at a wavelength of 412 nm for a duration of 2 min at 37 °C. To calculate the activity, a molar extinction coefficient (ε) of 17,100 $M^{-1}cm^{-1}$ was employed for p-nitrophenol in a 100 mM Tris-base buffer at pH 8.0. One unit of PON1 activity (1 UL^{-1}) was defined as the amount of enzyme required to generate 1 µmol of p-nitrophenol per minute [37, 41].

2.2.4 *In Vitro* Inhibition Studies

For inhibition studies, PON1 activity was measured in the presence of increasing concentrations of $CeVO_4$ derivatives. Enzymatic activity was determined spectrophotometrically by monitoring the hydrolysis of paraoxon under standard assay conditions. Eight different concentrations of each derivative were tested, and residual enzyme activity was calculated relative to a control sample lacking inhibitor, which was defined as 100% activity. To ensure statistical reliability, all experiments were performed in triplicate ($n = 3$) for each sample and concentration. Dose–response curves were constructed, and half-maximal inhibitory concentration (IC_{50}) values were obtained from regression analysis [40–43].

3 Results

The structural integrity of the doped $CeVO_4$ derivatives was confirmed by X-ray diffraction (XRD) analysis, as reported previously [36]. The diffraction patterns of Be-, Mg-, Ca-, Sr-, and Ba-doped $CeVO_4$ at doping ratios ranging from 0.1% to 10% were consistent with the characteristic reflections of undoped $CeVO_4$, and no secondary impurity phases were detected.

The inhibitory effects of alkaline earth metal–doped $CeVO_4$ derivatives on purified human PON1 were evaluated by determining IC_{50} values derived from concentration–response curves. All tested derivatives exhibited measurable inhibitory activity toward PON1, with IC_{50} ranging from 116.85 ± 2.531 µM to 212.71 ± 6.342 µM (Table 1). Among the tested compounds, the 10% Mg-doped $CeVO_4$ derivative demonstrated the most potent inhibition with an IC_{50} of 116.85 ± 2.531 µM. Similarly, 10.0% Ba-doped $CeVO_4$ exhibited a comparable and strong inhibitory effect (IC_{50} = 117.74 ± 2.056 µM). In contrast, Ca-doped derivatives showed a distinct and inverse trend; their IC_{50}

Table 1 IC_{50} values of alkaline earth metal–doped CeVO4 derivatives against PON1 paraoxonase activity

Compound	Doping (%)	IC_{50} (μM ± SD)	Compound	Doping (%)	IC_{50} (μM ± SD)
Be–$CeVO_4$	0.1	134,86 ± 2804	Sr–$CeVO_4$	0.1	154,92 ± 3842
	0.5	130,74 ± 2115		0.5	151,84 ± 3124
	1.0	124,87 ± 3074		1.0	150,71 ± 2956
	2.0	123,91 ± 2451		2.0	144,76 ± 3415
	4.0	122,84 ± 1987		4.0	138,62 ± 2841
	6.0	121,75 ± 2056		6.0	134,71 ± 2124
	8.0	120,12 ± 1842		8.0	133,84 ± 2451
	10.0	118,94 ± 1754		10.0	129,75 ± 2187
Mg–$CeVO_4$	0.1	147,82 ± 3941	Ba–$CeVO_4$	0.1	173,81 ± 4651
	0.5	146,75 ± 3124		0.5	159,84 ± 3842
	1.0	139,91 ± 2845		1.0	147,75 ± 3124
	2.0	133,82 ± 2541		2.0	141,84 ± 2987
	4.0	127,91 ± 2114		4.0	133,78 ± 3539
	6.0	124,84 ± 1987		6.0	123,91 ± 2114
	8.0	121,76 ± 2056		8.0	119,84 ± 1842
	10.0	116,85 ± 2531		10.0	117,74 ± 2056
Ca–$CeVO_4$	0.1	131,84 ± 3124			
	0.5	150,35 ± 3629			
	1.0	157,91 ± 4115			
	2.0	163,84 ± 4874			
	4.0	170,75 ± 5214			
	6.0	187,82 ± 4651			
	8.0	196,84 ± 5124			
	10.0	212,71 ± 6342			

increased progressively with higher doping ratios, reaching a maximum of 212.71 ± 6.342 μM at 10% substitution, indicating a decrease in inhibitory potency. Be- and Sr-doped derivatives displayed moderate inhibitory profiles, characterized by a gradual enhancement in inhibition as the doping percentage increased from 0.1% to 10.0%.

The inhibitory effects of synthesized $CeVO_4$ derivatives containing alkaline earth metal additives on purified human serum PON1 enzyme were examined in detail in the presence of 1 mM paraoxon substrate (Figs. 2 and 3). According to the data obtained, it was observed that all derivatives inhibited enzyme activity in a concentration-dependent manner; in particular, it was found that an increase in the metal doping ratio led to a significant decrease in the enzyme's paraoxonase activity. Upon analysis of the inhibition profiles, it is clearly evident from the dose-response curves in Fig. 2 that Be- and Mg-doped derivatives exhibit high affinity even at low concentrations, reducing activity below 50%, whereas Ca-doped derivatives exhibit higher IC_{50} values.

These results demonstrate that the ionic radius and electronic structure of the dopant play a critical role in modulating the catalytic interactions at the active site of the PON1 enzyme. To provide a more comprehensive analysis of the inhibitory behavior, individual activity-concentration curves for each alkaline earth metal-doped $CeVO_4$ derivative were generated using a 1 mM paraoxon substrate. While the consolidated comparison is shown in Fig. 1, the detailed separate graphs for each specific dopant (Be, Mg, Ca, Sr, and Ba) are provided in the Supporting Information.

The observed differences in inhibitory potency among doped derivatives indicate that both dopant type and concentration influence PON1 inhibition under the experimental conditions employed. The calculated IC_{50} values for all tested derivatives are summarized in Table 1.

4 Discussion

The present study demonstrates that alkaline earth metal–doped $CeVO_4$ derivatives exert concentration-dependent inhibitory effects on human serum PON1 activity. The observed differences in IC_{50} values among doped derivatives indicate that both dopant identity and substitution ratio influence the extent of enzyme inhibition under the applied experimental conditions.

The IC_{50} values determined in this study (116,85–212,71 μM) indicate moderate inhibitory potency under the applied *in vitro* conditions. Although these values fall within the micromolar range, $CeVO_4$ derivatives represent inorganic solid-state materials rather than classical small-molecule inhibitors, making direct comparisons of inhibitory strength inappropriate. In the context of metal oxide–enzyme interaction studies, micromolar IC_{50} values are commonly reported

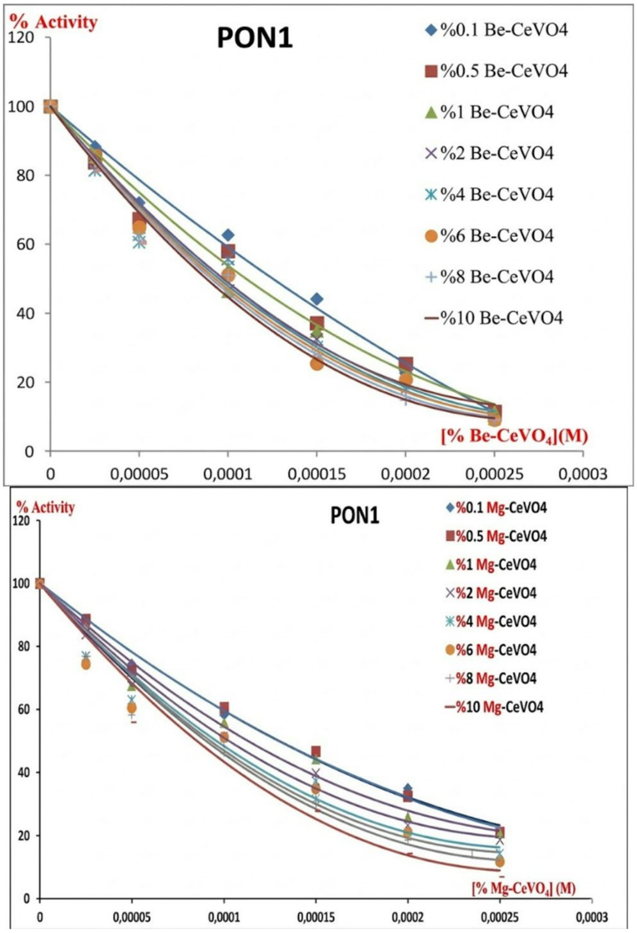

Fig. 2 % activity graph for % Be and Mg-doped CeVO$_4$ at a 1 mM concentration of the paraoxon substrate on purified human serum PON1 enzyme

and are considered sufficient to demonstrate meaningful enzyme interaction. Notably, the aim of the present work was not to identify high-affinity pharmacological inhibitors, but to comparatively assess dopant-dependent trends in PON1 inhibition. From this perspective, the observed IC$_{50}$ range clearly reflects concentration-dependent interaction and underscores the influence of alkaline earth metal substitution. Further studies will be required to evaluate the relevance of these findings under physiologically representative conditions.

A notable finding was the enhanced inhibitory potency observed with increasing doping levels in Mg- and Ba-substituted CeVO$_4$ derivatives, whereas Ca-doped materials displayed an opposite trend, with progressively higher IC$_{50}$ values at elevated substitution ratios. These variations suggest that structural modifications introduced by specific alkaline earth metals may alter the interaction dynamics between CeVO$_4$ surfaces and the catalytic region of PON1.

PON1 is a calcium-dependent enzyme containing two Ca^{2+} ions within its three-dimensional structure: one contributing to structural stability and the other directly involved in catalysis. The catalytic calcium ion participates in substrate orientation and stabilization of transition states during hydrolysis reactions [44]. Given this calcium-dependent mechanism, it is plausible that alterations in local ionic environment or surface charge distribution induced by doped CeVO$_4$ derivatives may influence enzyme–inhibitor interactions. However, the present data do not allow definitive conclusions regarding the precise molecular mechanism of inhibition.

Vanadate species are known to act as structural mimetics of phosphate groups, and phosphate analogues have been reported to interact with catalytic sites of phosphoesterases [45]. In this context, the VO$_4^{3-}$ moiety within CeVO$_4$ may contribute to competitive or coordination-based interference with the paraoxon hydrolysis process. Differences in ionic radius among Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} may further modulate lattice parameters and surface reactivity, thereby affecting accessibility or affinity toward the enzyme's active region. Nevertheless, these interpretations remain hypothetical and warrant confirmation through structural or computational studies.

It should be noted that beryllium-containing materials are known to raise safety concerns due to their potential toxicity, particularly under conditions of prolonged exposure [46]. In the present study, Be-doped CeVO$_4$ derivatives were included solely for comparative and mechanistic evaluation within a controlled *in vitro* framework. No therapeutic or biomedical application is implied for beryllium-containing derivatives, and any potential biological relevance would require rigorous toxicological assessment. Accordingly, the inclusion of Be serves to highlight dopant-dependent effects rather than to suggest suitability for *in vivo* use.

From a broader perspective, modulation of PON1 activity by engineered metal oxide derivatives may have implications in oxidative stress–related and toxicological settings. While the inhibitory effects observed provide mechanistic insight into CeVO$_4$–enzyme interactions, further investigations are required to determine their biological relevance, specificity, and safety *in vivo*.

5 Conclusions

This study demonstrated that alkaline earth metal–doped cerium vanadate (CeVO$_4$) derivatives exert measurable and concentration-dependent inhibitory effects on human serum paraoxonase-1 (PON1) paraoxonase activity *in vitro*. The observed variation in IC$_{50}$ values among Be-, Mg-, Ca-, Sr-, and Ba-doped CeVO$_4$ derivatives indicates that both dopant type and substitution level influence the extent of enzyme inhibition.

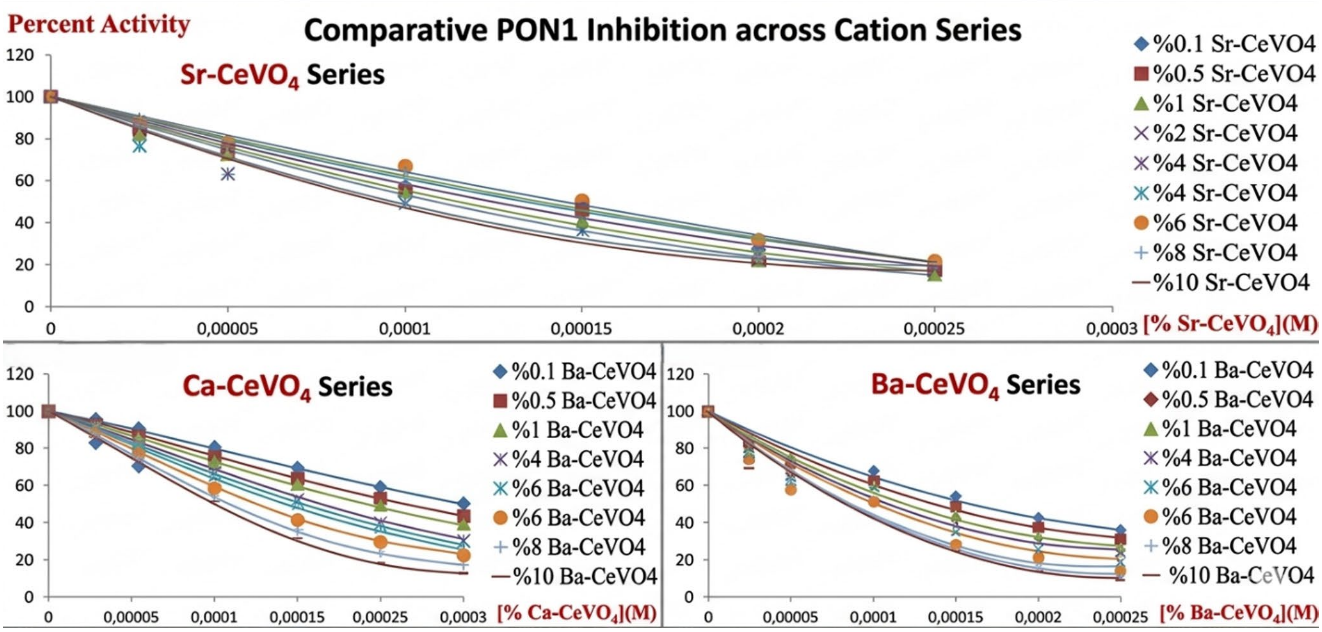

Fig. 3 % activity graph for % Ca, Ba and Sr-doped CeVO₄ at a 1 mM concentration of the paraoxon substrate on purified human serum PON1 enzyme

Notably, Mg- and Ba-doped CeVO$_4$ derivatives exhibited stronger inhibitory effects at higher doping ratios, whereas Ca-doped derivatives showed reduced inhibitory potency with increasing substitution. These findings suggest that structural and physicochemical modifications introduced by specific alkaline earth metals play a role in modulating CeVO$_4$–PON1 interactions.

While the present results provide insight into the inhibitory behavior of CeVO$_4$ derivatives toward PON1 under *in vitro* conditions, further studies are required to elucidate the precise molecular mechanisms underlying these interactions and to assess their biological relevance. In particular, comprehensive kinetic analyses and *in vivo* investigations will be necessary to evaluate specificity, safety, and potential toxicological implications.

Overall, the findings contribute to a better understanding of metal oxide–enzyme interactions and highlight the importance of considering dopant-dependent effects when evaluating the biological activity of engineered vanadate-based materials.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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